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Ambient Water Quality Criteria: Benzene

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for benzene. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no r , ...

KEYWORDS: *Water quality, *Toxicology, *Benzene, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances.

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BENZENE

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERION DOCUMENT

BENZENE

CRITERIA

Aquatic Life

For benzene the criterion to protect freshwater aquatic life as derived using the Guidelines is 3,100 µg/l as a 24-hour average and the concentration should not exceed 7,000 µg/l at any time.

The data base for saltwater aquatic life is insufficient to allow use of the Guidelines. The following recommendation is inferred from toxicity data for freshwater organisms.

For benzene the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 920 µg/l as a 24-hour average and the concentration should not exceed 2,100 µg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to benzene through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of benzene estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the criterion formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 15 µg/l, 1.5 µg/l, and 0.15 µg/l, respectively.

Introduction

Benzene is a volatile, colorless, liquid hydrocarbon produced principally from coal tar distillation and from petroleum by catalytic reforming of light naphthas from which it is isolated by distillation or solvent extraction (Weast, 1972; Ayers and Muder, 1964; U.S. EPA, 1976). It is also produced in coal processing and coal coking operations. The broad utility spectrum of benzene (commercially sometimes called "Benzol") includes its use as: an intermediate for synthesis in the chemical and pharmaceutical industries including the manufacture of styrene, cyclohexane, detergents, and pesticides, a thinner for lacquers, a degreasing and cleaning agent, a solvent in the rubber industry, an antiknock fuel additive, a general solvent in laboratories, a solvent for industrial extraction and rectification, and in the preparation and use of inks in the graphic arts industries.

In the United States today, benzene is used extensively (over 4 million metric tons annually) in the chemical industry and its use is expected to increase when additional production facilities become available (Fick. 1976).

Benzene has the molecular formula C_6H_6 and a molecular weight of 78.1 (Weast, 1972; Ayers and Muder, 1964). Pure benzene has a boiling point of 80.1 degrees C and a melting point of 5.5 degrees C (Weast, 1972). Benzene has a density less than that of water (0.87865 at 20 degrees C) and is soluble in water at concentrations which have been shown to be toxic to aquatic organisms (Weast, 1972; Stecher, 1968). Benzene is also readily soluble in natural fats

and fat soluble substances (Weast, 1972). It may bioaccumulate in living organisms and appears to accumulate in animal tissues that exhibit a high lipid content or represent major metabolic sites such as liver and brain. The solubility and volatile nature of benzene indicate possible environmental mobility. Benzene has been detected at various concentrations in lakes and streams, finished drinking water, and is a leukemic agent in humans. While animal studies have been negative, human case histories and epidemiological studies have provided confirmatory evidence of the causal relationship of benzene exposure to leukemia.

Benzene has also been demonstrated to affect aquatic life adversely. Reproductive impairment has been observed in fish at benzene concentrations well below the lethal level. Benzene in the environment has been demonstrated to exert deleterious effects at many levels of the food chain.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Most of the freshwater data concerning the effects of benzene on aquatic life have been determined using static test conditions. Consequently, these data may underestimate the toxicity of this volatile chemical. Nearly all of the adverse acute and chronic effects occurred at concentrations above 20,000 µg/l.

Acute Toxicity

Five fish species have been tested (Table 1) and the LC50 values are between 20,000 and 36,600 µg benzene/l for the goldfish, fathead minnow, guppy, and bluegill. The 96-hour LC50 for the mosquitofish is 38o,000 µg/l (Wallen, et al. 1957). After adjusting the geometric mean LC50 of 27,200 µg/l by the sensitivity factor of 3.9, the Final Fish Acute Value is calculated to be 7,000 µg/l.

Daphnia magna is the only invertebrate species that has been tested (U.S. EPA, 1978) and the 48-hour EC50 is 203,000 µg/l. The Final Invertebrate Acute Value calculated from this result is 8,200 µg/l (Table 2). Consequently, the Final Acute Value, the lower of the Final Fish and Invertebrate Acute Values, is 7,000 µg/l.

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following summary and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Chronic Toxicity

A chronic test with Daphnia magna was conducted (U.S. EPA, 1978) but the results were incomplete. No adverse effects were observed at test concentrations as high as 98,000 µg/l. Since the adjusted 48-hour EC50 value is 172,000 µg/l, there is little difference between the acute and chronic effects of benzene on Daphnia magna. The Final Invertebrate Chronic Value is greater than 19,000 µg/l after dividing the experimental value by the sensitivity factor of 5.1 (Table 3). It is interesting to note that this Final Invertebrate Chronic Value, based on Daphnia magna, is higher than the Final Invertebrate Acute Value, which was based on the same species. This relationship can be explained by the small difference discussed earlier, between the acute and chronic effects and the fact that the acute sensitivity factor for invertebrate species (21) is about four times larger than that for chronic data (5.1).

Plant Effects

The Final Plant Value (Table 4) is 530,000 µg/l based on the data of Kauss and Hutchinson (1975) who determined that there was a 50 percent reduction in the cell numbers of Chlorella vulgaris after 48 hours at that concentration.

Residues

No measured steady-state bioconcentration factor (BCF) is available for benzene. A BCF can be estimated using the octanol-water partition coefficient of 132. This coefficient is used to derive an estimated BCF of 24 for aquatic organisms that contain about 8 percent lipids. If it is

known that the diet of the wildlife of concern contains a significantly different lipid content, an appropriate adjustment in the estimated BCF should be made.

Miscellaneous

The only additional experimental information is for a short exposure of brown trout to lethal concentrations of benzene (Table 5). The LC50 value was 12,000 µg/l.

CRITERION FORMULATION

Freshwater Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 7,000 µg/l

Final Invertebrate Acute Value = 8,200 µg/l

Final Acute Value = 7,000 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = greater than 19,000 µg/l

Final Plant Value = 530,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = greater than 19,000 µg/l

0.44 x Final Acute Value = 3,100 µg/l

The maximum concentration is the Final Acute Value of 7,000 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For benzene the criterion to protect freshwater aquatic life, as derived using the Guidelines, is 3,100 µg/l expressed as a 24-hour average and the concentration should not exceed 7,000 µg/l at any time.

Table 1. Freshwater fish acute values for benzene

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Goldfish, *Carassius auratus*	S	U	96	34,420	18,820	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S	U	96	33,470	18,300	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S	U	96	32,000	17,490	Pickering & Henderson, 1966
Guppy, *Poecilia reticulatus*	S	U	96	36,600	20,010	Pickering & Henderson, 1966
Mosquitofish, *Gambusia affinis*	S	U	96	386,000	211,000	Wallen, et al. 1957
Bluegill, *Lepomis macrochirus*	S	U	96	22,490	12,300	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S	U	48	20,000	8,900	Turnbull, et al. 1954

* S = static

** U = unmeasured

Geometric mean of adjusted value = 27,200 µg/l $\quad \frac{27,200}{3.9} = 7,000$ µg/l

Table 2. Freshwater invertebrate acute values for benzene (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Cladoceran, *Daphnia magna*	S	U	48	203,000	172,000

* S = static

** U = unmeasured

Geometric mean of adjusted values = 172,000 µg/l $\frac{172,000}{21}$ = 8,200 µg/l

Table 3. Freshwater invertebrate chronic values for benzene (U.S. EPA, 1978)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)
Cladoceran, *Daphnia magna*	LC	>98,000	>98,000

* LC = life cycle or partial life cycle

Geometric mean of chronic value = >98,000 µg/l $\quad \frac{>98,000}{5.1} = >19,000$ µg/l

Lowest chronic value = >98,000 µg/l

Table 4. Freshwater plant effects for benzene (Kauss & Hutchinson, 1975)

Organism	Effect	Concentration (µg/l)
Alga, *Chlorella vulgaris*	EC50 48 hr 50% reduction in cell numbers	525,000

Lowest plant value = 525,000 µg/l

Table 5. Other freshwater data for benzene (Woodiwiss & Fretwell, 1974)

Organism	Test Duration	Effect	Result (µg/l)
Brown trout, *Salmo trutta*	1 hr or 24 hrs	LC50	12,000

SALTWATER ORGANISMS

Introduction

As with the data base for freshwater organisms, the saltwater organism data base is limited and predominantly derived using static test procedures. Most LC50 and plant values are between 5,000 and 100,000 µg/l. However, some data (Struhsaker, 1977) in Table 9 indicate that unique acute effects may occur at benzene concentrations as low as 700 µg/l.

Acute Toxicity

The striped bass, anchovy, and Pacific herring have been exposed to benzene and the LC50 values are between 5,800 and 25,000 µg/l (Table 6). These species and the life stages studied appear to be similarly sensitive to benzene. The Final Fish Acute Value derived from these data is 2,400 µg/l. The tested invertebrate species appear to be less sensitive (Table 7) than the fish. The LC50 values ranged from 27,000 µg/l for the grass shrimp (Tatem, 1975) to 450,000 µg/l for a copepod (Korn, et al. 1976). However, since the sensitivity factor for saltwater invertebrates is greater than that for saltwater fish, the Final Invertebrate Acute Value is lower than that for fish. Thus, the Final Invertebrate Acute Value, 2,100 µg/l, is lower than that for fish and becomes the Final Acute Value.

Chronic Toxicity

The chronic effects of benzene on saltwater fish and invertebrates have not been studied.

Plant Effects

Three algal or diatom species have been tested (Dunstan, et al. 1975; Atkinson, et al. 1977) and growth was inhibited at benzene concentrations of 20,000 to 100,000 µg/l (Table 8). The Final Plant Value is 20,000 µg/l.

Residues

No measured steady-state bicconcentration factor (BCF) is available for benzene. A BCF can be estimated using the octanol-water partition coefficient of 132. This coefficient is used to derive an estimated BCF of 24 for aquatic organisms that contain about 8 percent lipids. If it is known that the diet of the wildlife of concern contains a significantly different lipid content, an appropriate adjustment in the estimated BCF should be made.

Miscellaneous

Struhsaker (1977) exposed female Pacific herring to 700 µg/l for 48 hours just prior to their spawning. Survival of embryos at hatching and survival of larvae through yolk absorption were reduced (Table 9). The results of this study need further verification before such effects may be used to derive a criterion for saltwater organisms. Only one test concentration was used to determine the effects of benzene on survival of embryos and larvae; no slope or no-effect concentration was determined. Also the adult fish were captured from San Francisco Bay waters which, as stated by the authors, may affect the hatchability of Pacific herring eggs due to the effects of accumulated pollutants in the gonads.

CRITERION FORMULATION

Saltwater Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 2,400 µg/l

Final Invertebrate Acute Value = 2,100 µg/l

Final Acute Value = 2,100 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 20,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 20,000 µg/l

0.44 x Final Acute Value = 920 µg/l

No saltwater criterion can be derived for benzene using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

However, results obtained for benzene with freshwater organisms indicate how a criterion may be derived. For benzene and freshwater organisms the Final Chronic Value based on Daphnia magna is greater than 0.44 times the Final Acute Value. Therefore, it seems reasonable to derive a criterion for benzene and saltwater organisms using 0.44 times the Final Acute Value.

The maximum concentration is the Final Acute Value of 2,100 µg/l and the estimated 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse

effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration other than those noted earlier (Struhsaker, 1977).

CRITERION: For benzene, the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 920 µg/l as a 24-hour average and the concentration should not exceed 2,100 µg/l at any time.

Table 6. Marine fish acute values for benzene

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Pacific herring (larva), Clupea pallasi	S	U	48	20,000-25,000	9,906	Struhsaker, et al. 1974
Anchovey (larva), Engraulis mordes	S	U	48	20,000 25,000	9,906	Struhsaker, et al. 1974
Striped bass, Morone saxatilis	FT	M	96	10,900	10,900	Meyerhoff, 1975
Striped bass, Morone saxatilis	S	M	96	5,800	4,118	Benville & Korn, 1977

* S = static, FT = flow-through
** U = unmeasured, M = measured
Geometric mean of adjusted values = 8,695 µg/l $\frac{8,695}{3.7}$ = 2,400 µg/l

Table 7. Marine invertebrate acute values for benzene

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Copepod, Tigriopus californicus	S	M	96	450,000	495,000	Korn, et al. 1976
Grass shrimp, Palaemonetes pugio	S	U	96	27,000	22,869	Tatem, 1975
Dungeness crab (larva), Cancer magister	S	U	96	108,000	91,476	Caldwell, et al. 1977

* S = static

** U = unmeasured, M = measured

Geometric mean of adjusted values = 101,170 ug/l $\frac{101,170}{49}$ = 2,100 ug/l

Table 8. Marine plant values for benzene

Organism	Effect	Concentration (µg/l)	Reference
Dinoflagellate, *Amphidinium carterae*	Growth inhibition	>50,000	Dunstan, et al. 1975
Diatom, *Skeletonema costatum*	Growth inhibition	100,000	Dunstan, et al. 1975
Alga, *Cricosphaera carterae*	Growth inhibition	50,000	Dunstan, et al. 1975
Diatom, *Skeletonema costatum*	Growth inhibition	20,000	Atkinson, et al. 1977

Lowest plant value = 20,000 µg/l

Table 9. Other marine data for benzene

Organism	Test Duration	Effect	Result (µg/l)	Reference
Pacific herring, *Clupea harengus pallasi*	144 hrs	Stress observed	700	Struhsaker, 1977
Pacific herring, *Clupea harengus pallasi*	168 hrs	Survival reduction in	700	Struhsaker, 1977
Striped bass, *Morone saxatilis*	168 hrs	Temporary weight reduction	6,000	Korn, et al. 1976

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Mammalian Toxicology and Human Health Effects

Exposure

Ingestion. Benzene is soluble in water (1,780 mg/l at 25°C) but human exposure through food and water is difficult to quantify because of a relative paucity of data. Four of ten water supplies surveyed by the EPA contained benzene at concentrations of 0.1 to 0.3 µg/l; the highest concentration ever reported in a finished water was 10 µg/l (Natl. Acad. Sci./Natl. Res. Coun., 1977).

Only limited data on benzene in water are available. A review of benzene sampling data by Howard and Durkin (1974) found that the few freshwater samples analyzed by that time showed only trace levels of benzene. For example, a 1972 EPA study cited in the report identified 53 organic chemicals, ranging from acetone to toluene, in the finished waters and organic waste effluents in 11 plants (of 60 sampled) discharging into the Mississippi River. Benzene was not detected in the effluents, but the trace detected in the finished waters suggested another source than effluent discharge.

A recent sampling of five benzene production or consumption plants by Battelle (1977a) found benzene levels in water ranging from < 1.0 to 179 ppb (plant effluent). The concentrations at 13 upstream and downstream sample locations in nearby receiving waters, however, ranged from < 1.0 to 13.0 ppb, with an average of 4.0 ppb.

A recent report by the National Cancer Institute (1977) noted benzene levels of 0.1 to 0.3 ppb in four U.S. city drinking water supplies. One measurement from a groundwater well in Jacksonville, Florida showed levels higher than 100 ppb. No indication is given in the report of the sampling methods or the analytical procedures.

One possible source of benzene in the aquatic environment is from cyclings between the atmosphere and water (Mitre, 1976). Benzene is fairly volatile (high vapor pressure of 100 mm Hg at 26°C) and has a relatively high solubility (1,780 mg/l* at 25°C). Consequently, it is reasonable to believe that benzene could be washed out of the atmosphere with rainfall and then evaporated back into the atmosphere, causing a continuous recycling between the two media.

The exposure to benzene through general dietary intake is not considered to be a problem of the general population. However, benzene has been detected in various food categories: fruits, nuts, vegetables, dairy products, meat, fish, poultry, eggs and several beverages; an indication of this has been tabulated by the National Cancer Institute (1977).

ESTIMATED BENZENE LEVELS IN FOOD
(g/kg)

Heat treated or canned beef	2
Jamaican rum	120
Irradiated beef	19
Eggs	500-1900

NCI estimated that an individual could ingest as much as 250 µg/day from these foods.

The distribution of benzene in the aquatic system is not well documented. Neely, et al. (1974) demonstrated a relationship between octanol - water partition coefficients and bioaccumulation potential in fish. To protect humans, health water quality criterion should apply to saltwater as well as freshwater because the major portion of the aquatic life consumed in the United States is obtained from saltwater.

A bioconcentration factor (BCF) relates the concentration of chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

No measured steady-state bioconcentration factor (BCF) is available for benzene, but the equation "Log BCF = 0.76 Log P - 0.23" can be used (Veith, et al. Manuscript) to estimate the BCF for aquatic organisms that contain about 8 percent lipids from the octanol-water partition coefficient (P). Based on an octanol-water partition coefficient of 132, the steady-state bioconcentration factor for benzene is estimated to be 24. An adjustment factor of 2.3/8.0 = 0.2875 can be used to adjust the estimated BCF from the 8.0 percent lipids on which the equation is based to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for benzene and the edible portion of all aquatic organisms consumed by Americans is calculated to be 24 x 0.2875 = 6.9.

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Inhalation. The respiratory route is the major source of human exposure to benzene, and much of this exposure is by way of gasoline vapors and automotive emissions. American gasolines contain an average of 0.8 percent (by weight) benzene, and European gasolines contain an average of 5 percent (Goldstein, 1977a). Automotive exhausts contain an average of 4 percent (by weight) benzene (Howard and Durkin, 1974). Total motor vehicle emissions make up well over half of the benzene released to the environment; this distribution probably approximates population density distribution. Release from industrial and commercial use probably does not exceed 30 percent of the total. Other sources are relatively insignificant (Howard and Durkin, 1974).

Concentrations of benzene in the ambient air of gas stations have been found to be 0.3 to 2.4 ppm (Natl. Acad. Sci./Natl. Res. Coun., 1977). Lonneman, et al. (1968) measured an average

concentration of 0.015 ppm in Los Angeles air, with a maximum of 0.057 ppm. The rural background level for benzene has been reported as 0.017 ppb (Cleland and Kingsbury, 1977). On the basis of production data for benzene and its major products, emission factors, air dispersion models, and population density information, Mara and Lee (1977) calculated that the annual average exposure of an individual to ambient benzene from all sources is 1.03 ppb. Recently, Young, et al. (1978) have brought attention to the fact that consumers may be exposed unknowingly to benzene in the home in the form of paint strippers, carburetor cleaners, denatured alcohol, rubber cement, and art and craft supplies.

Dermal. Since liquid benzene is poorly absorbed through the intact skin (Natl. Inst. Occup. Safety Health, 1974) and skin contact is infrequent, the dermal route is only a minor source of human exposure.

Pharmacokinetics

Absorption. The respiratory absorption of benzene by humans has been measured several times. Duvoir, et al. (1946) estimated an absorption rate of 28 to 34 percent in humans exposed to 6,000 ppm. Srbova, et al. (1950) found 40 to 50 percent retained on exposure to 47 to 110 ppm. Teisinger, et al. (1952) found 46 percent absorption on exposure to 100 ppm. Hunter (1966) found 47 percent absorption on exposure to 35 ppm. Hunter and Blair (1972) found that humans retain approximately 230 mg of benzene

from exposure to 80 to 100 µg/l (24 to 30 ppm) for 6 hours. Nomiyama and Nomiyama (1974a) found 47 percent respiratory uptake, with simultaneous 17 percent respiratory excretion on exposure to 52 to 62 ppm benzene for 4 hours.

The dermal absorption of benzene by humans has been measured by Hanke, et al. (1961), who found a rate of 0.4 mg/cm^2/hr of liquid benzene applied under a closed cup.

Deichmann, et al. (1963) exposed rats to an average of 47 ppm benzene vapor. Blood benzene levels ranged between 1.624 to 8.70 mg/l (mean = 4.2 mg/l) after 180 days of exposure to the vapor. Rats exposed to 44 ppm for up to 54, 7-hour periods maintained a blood benzene level range of 3.2 to 6.7 mg/l (mean = 4.31 mg/l).

Distribution. Free benzene accumulates in lipid tissue such as fat and bone marrow, and benzene metabolites accumulate in liver tissue and bone marrow (U.S. EPA, 1977).

Metabolism. The metabolism of benzene has been reviewed by Rusch, et al. (1977). The initial step appears to be a reaction mediated by the mixed-function oxidase. This enzyme is inducible, so that pretreatment with benzene, phenobarbital, or 3-methylcholanthrene can increase the rate of benzene metabolism. The direct product of the interaction of benzene with mixed-function oxidase is probably an arene oxide that is highly reactive. It can spontaneously rearrange to form phenol, undergo enzymatic hydration followed by dehydrogenation to form catechol

or a glutathione derivative (phenylmercapturic acid), or bind covalently with cellular macromolecules. Formation of hydroquinone or of trihydroxylated compounds probably is the result of several reactions with hydroxylating enzymes. Benzene is excreted in the urine in the form of sulfate and glucuronide conjugates of many of these compounds, particularly phenol. See Figure 1 for an illustration of the metabolic pathway.

Evidence has accumulated that a metabolite of benzene is responsible for benzene toxicity. Nomiyama (1964) demonstrated that inhibition of benzene metabolism protected rats against benzene-induced leukopenia. Andrews, et al. (1977) reported that when benzene metabolism was inhibited with toluene the subjects were protected against benzene-induced reduction of red cell production. Animals have been protected against benzene toxicity when pretreated with phenobarbital (Drew, et al. 1974; Ikeda, et al. 1972), probably because phenobarbital stimulates benzene metabolism in the liver, which leads to detoxification and thereby reduces the amount of benzene available for formation of the toxic agent in bone marrow. The specific metabolite that produces benzene toxicity has not yet been identified, but likely candidates are benzene oxide, catechol, and hydroquinone, or the corresponding semiquinones (U.S. EPA, 1977).

Teisinger, et al. (1952) exposed humans to benzene at 100 ppm for 5 hours and reported that 46 percent of the dose was retained. Of that amount, 61 percent was recovered as phenol, 6.3 percent as catechol, and 2.4 percent as hydroquinone.

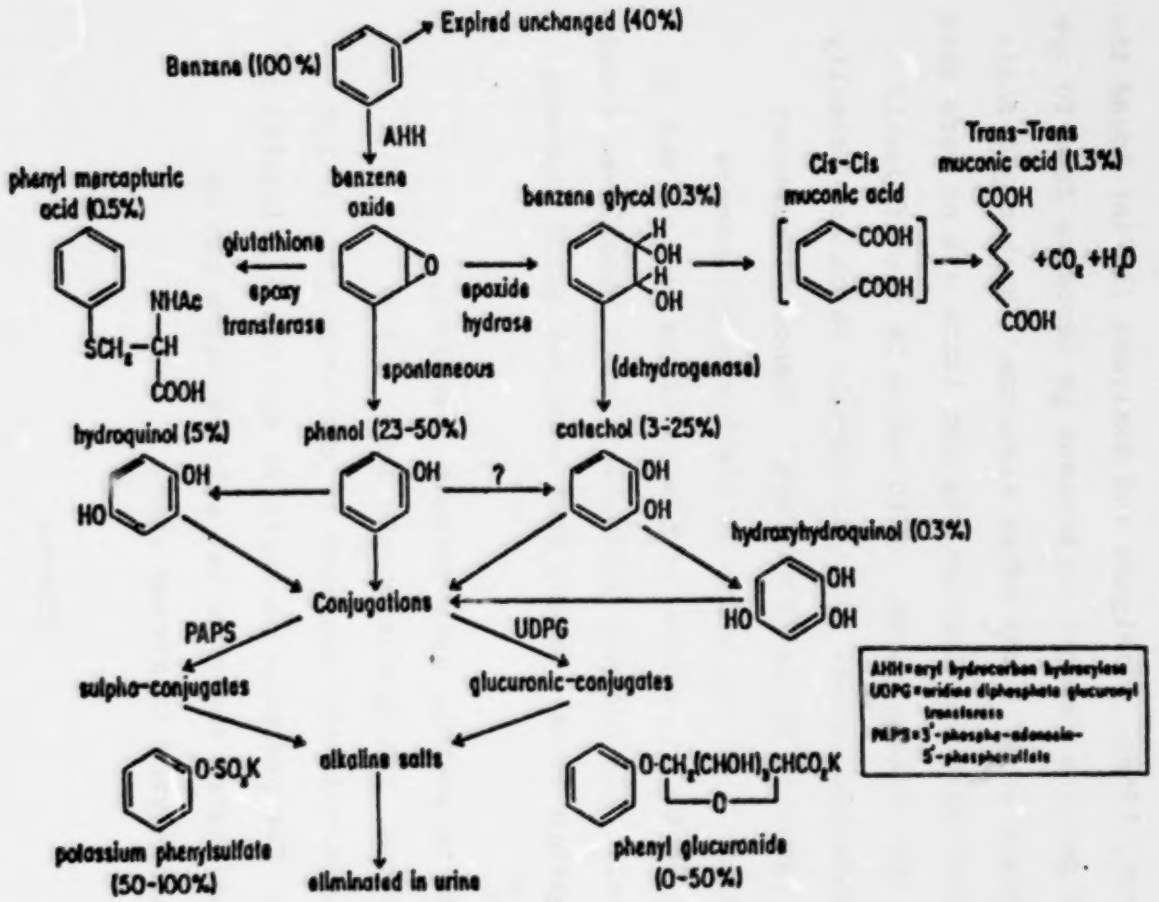

Figure 1. Metabolic pathway of benzene in liver.

(Forni, Pacifico, Limonta, 1971)

Excretion. Respiratory excretion of absorbed benzene occurs rapidly, and can be detected for 24 hours after a 100 ppm exposure (Hunter, 1968). Nomiyama and Nomiyama (1974b) found the expired air of persons exposed to benzene to decrease from 10 ppm to 0.5 ppm benzene in 17 hours after exposure. Hunter and Blair (1972) determined that elimination via the lungs was no more than 12 percent of the retained dose. This value is significantly less than elimination losses found in animals which are normally quoted in the range of 50 to 70 percent. Phenol measurement (free plus combined) of the urine of the human volunteers indicated that 50 to 87 percent of the retained benzene was excreted as phenol. The highest concentration of phenol was found in the urine within about 3 hours from termination of exposure.

In addition to phenol, hydroquinone, catechol, hydroxhydroquinone, transtransmuconic acid, and L-phenylmercapturic acid are excreted in the urine (Snyder and Kocsis, 1975). The phenolic metabolites are found primarily as glucuronide conjugates and ethereal sulfate which can be liberated by hydrolysis in strong acid.

Effects

Toxicity. In man, acute benzene poisoning is characterized by nausea, vomiting, ataxia, and excitement,, followed by depression and coma. Death is usually the result of respiratory or cardiac failure (Holvny, 1972). Benzene exposure causes acute toxic effects on the central nervous system. These have been

reviewed by Gerarde (1960) and Browning (1965). Single exposures to benzene in the air at a concentration of 20,000 ppm have proved to be fatal within 5 to 10 minutes. Effects included headache, nausea, staggering gait, paralysis, convulsions, and eventual unconsciousness and death, usually following cardiovascular collapse. Giddiness and euphoria have also been reported. Severe non-fatal cases have exhibited similar symptoms, but recovered after a period of unconsciousness. Autopsy findings have indicated respiratory tract inflammation, lung hemorrhages, kidney congestion, and cerebral edema (Winek and Collom, 1971).

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It has also been suggested that ingested benzene causes acute toxic effects on the gastrointestinal system (Appuhn and Goldeck, 1957; Caprotti, et al. 1962).

The chronic effects of benzene have recently been thoroughly reviewed by the Natl. Acad. Sci./Natl. Res. Coun. (1976) and the U.S. EPA (1977). These reports have served as the main source of data for this section and the sections on mutagenicity and carcinogenicity.

The hundreds of references describing human hematological toxicity associated with benzene exposure have been reviewed by Browning (1965), Goldstein (1977b), Int. Labour Off. (1968), Natl. Inst. Occup. Safety Health (1974, 1977), and Snyder and Kocsis (1975). Numerous hematological disorders have been reported to be associated with benzene exposure. However, only two disorders are clearly related to benzene: (1) pancytopenia

and its variants, e.g., anemia, leukopenia, thrombocytopenia, and aplastic anemia; and (2) acute myelogenous leukemia (AML) and its variants, e.g., acute myelomonocytic leukemia and erythroleukemia. (AML is discussed in the section on carcinogenicity.) The symptoms of pancytopenia in individuals exposed to benzene tend to appear gradually, and presumably reflect anemia, e.g., lassitude, easy fatigability, malaise, dizziness, headaches, palpitation, and shortness of breath. In severe cases, death is often due to hemorrhage caused by thrombocytopenia or decreased platelet function, or to overwhelming infection caused by leukopenia (U.S. EPA, 1977). Patients with pancytopenia may also subsequently develop AML.

The bone marrow in pancytopenia usually shows a decreased cellularity, including absence of megakaryocytes, and a dominance of the most immature forms of red and white cells. The course of the hypoplastic marrow effects may be progressive unless the person is removed from the benzene exposure and appropriate treatment administered. If this is done, complete recovery may follow, but the process is usually slow. Repeated exposures to benzene may result in more severe recurrences. Even without repeated exposure the condition may become irreversible and develop into chronic progressive pancytopenia, acute pancytopenia, or leukemia (Natl. Acad. Sci./Natl. Res. Coun., 1976).

Aksoy, et al. (1971) conducted a study on 217 workers who had been exposed to benzene in the workplace at concentrations

ranging between 30 to 210 ppm from 3 months to 17 years. When compared to 100 control subjects, 51 percent of the workers showed hematological abnormalities attributable to chronic benzene exposure. Leukopenia was detected in 9.7 percent of the workers; thrombocytopenia in 1.84 percent. Leukopenia associated with thrombocytopenia was found in 4.6 percent and leukopenia as a part of pancytopenia in 2.76 percent of the cases. Thus, 17.5 percent of the workers had a white cell count of less than 4,000/mm^3. Hemoglobin levels were less than 12 g/100 ml in 33 percent of the workers and in 32.7 percent the packed cell volume was less than 40 percent. While a mild or moderate hypochromic or normochromic anemia was present in 33 percent of the workers, the same result was found in 21 percent of the controls. Much of this anemia was considered to be caused by iron deficiency.

Chronic effects of benzene on the immunological system have been reported. Lange, et al. (1973a) found decreased levels of IgG and IgA and increased levels of IgM in workers exposed to a combination of benzene, toluene, and xylene. Some of these workers were found to have autoleukocyte agglutinins, suggesting the occurrence of an allergic blood dyscrasia in some people exposed to benzene and its homologs (Lange, et al. 1973b). Smolik, et al. (1973) have found significantly lower serum complement levels in workers exposed to benzene, toluene, and xylene.

Although the causal relationship between benzene exposure and human disorders is clear, the literature does not allow any

conclusions to be drawn on the dose-response relationship between benzene and these disorders in humans. Some dose-response data on the effects of benzene on animals, however, exist. Wolf, et al. (1956) reported that the no-effect level for blood changes in rats, guinea pigs, and rabbits was below 88 ppm in the air when the animals were exposed for 7 hr/day for up to 269 days. At this level slight leukopenia was observed in rats; leukopenia was also seen in rats given 132 daily oral doses of 10 mg/kg for 187 days. Jenkins, et al. (1970) found no effects on the blood composition of rats, quinea pigs, and dogs exposed continuously to 17.6 ppm benzene for up to 127 days. Slight leukopenia has been reported to occur in rats exposed to 44 ppm benzene for 5 hrs/day, 4 days/week for 5 to 7 weeks (Deichmann, et al. 1963). Deichmann, et al. (1963) exposed Sprague-Dawley rats to 15 to 831 ppm benzene vapor for 20 hours/week for 6 to 31 weeks. Rats exposed to a mean concentration of 65 ppm for 26 out of 39 days showed a decrease in white blood cell count after 2 weeks in males and after 4 weeks in female rats. Animals exposed to 47 ppm and 31 ppm exhibited abnormalities of the spleen and lungs. Rats exposed to 831 ppm for 32 of 46 days showed a decrease in white blood cell count that remained constant throughout the period of exposure.

Sprague-Dawley rats of different ages received oral doses of undiluted benzene to determine the oral LD50 (Kimura, et al. 1970). Acute LD50's reported are: immature rats, 3.4 mg/kg; young adult rats, 3.8 mg/kg; old adult rats, 5.6 mg/kg. A

concentration of 0.87 mg/kg body weight proved fatal to newborn rats.

Dobashi (1974) measured the cell renewal rate as well as the rate of DNA synthesis in cultured human leukocytes and HeLa cells exposed to benzene. Both cell types exhibited 50 percent inhibition of growth at 171.6 mg/l. The rate of DNA synthesis in leukocytes was inhibited by 50 percent at 171.6 mg/l, while in HeLa cells this effect occurred at 85.8 mg/l benzene.

Synergism and/or Antagonism. Most reports on the human health effects of benzene have originated in workers exposed to high concentrations of benzene in conjunction with other solvents, e.g., toluene and xylene. Thus it has been suggested that benzene might act synergistically with other compounds. Such a co-leukemogenic role for benzene might explain the failure to induce leukemia in animals (Natl. Acad. Sci./Natl. Res. Coun., 1976).

Teratogenicity. Gofmekler (1968) found complete absence of pregnancy in female rats exposed continuously to 209.7 ppm benzene for 10 to 15 days prior to impregnation. One of ten rats exposed to 19.8 ppm exhibited resorption of embryos, and the number of offspring per female exhibited an inverse relationship to benzene exposure levels from 0.3 to 209.7 ppm. The weights of the newborn rats were normal, but those from the 19.8 ppm exposure group had significantly larger liver, lung, spleen, and kidney weights. A small increase in fetal resorption occurred in

rats exposed to 10 to 40 ppm benzene during days 6 to 15 of gestation in one study, while no increase was observed after exposure to 100 to 2,200 ppm in another study (Am. Pet. Inst. 1978). In the latter study some skeletal deformities were observed in the newborn rats. Pregnant mice given single subcutaneous injections of benzene (3 ml/kg) on days 11 to 15 of gestation produced fetuses with cleft palates, agnathia, and micrognathia, when delivered by caesarian section on day 19 (Watanabe and Yashida, 1970).

Mutagenicity. Benzene has not shown mutagenic activity in the Salmonella/microsome in vitro assay (Lyon, 1975; Shahin, 1977; Simmon, et al. 1977). It has shown such activity, however, in animals and man. In rabbits injected subcutaneously with 0.2 mg/kg/day benzene, the frequency of bone marrow mitoses with chromosomal aberrations increased from 5.9 percent to 57.8 percent after an average of 18 weeks (Kissling and Speck, 1971). Dobrokhotov (1972) exposed rats to 0.2 g/kg/day benzene and 0.8 g/kg/day toluene individually and together, and found similar rates of chromosomal aberrations in the two chemicals given separately, and an additive effect when given together. Chromatid deletions in metaphase chromosomes of bone-marrow cells have been found in rats given single doses of subcutaneous benzene at 2 ml/kg (Philip and Jensen, 1970), and rats given subcutaneous benzene at 1 g/kg/day for 12 days (Lyapkalo, 1973). Lyon (1975) dosed rats with 0.5 ml/kg benzene intraperitoneally, and found no induced dominant lethality but increased chromatid and chromosomal abberrations. Lyon (1975) also found increased

micronuclei counts 6 hours after final dosing of rats at 0.05 and 0.25 ml/kg intraperitoneally on each of 2 successive days. Cultured human leukocytes have also exhibited chromosomal aberrations upon benzene exposure (Koizumi, et al. 1974; Haberlandt and Mente, 1971).

In patients with benzene-induced aplastic anemia, lymphocyte chromosome damage, i.e., abnormal karyotype and deletion of chromosomal material, has been found (Pollini and Colombi, 1964). Pollini, et al. (1964) later found a 70 percent incidence of heteroploid chromosomal patterns in the blood lympocytes and bone marrow parenchyma cells of each of four subjects with benzene-induced blood dyscrasia. Chromosomal alterations associated with benzene-induced blood dyscrasias have also been reported by others (Forni and Moreo, 1967, 1969; Hartwich, et al. 1969; Khan and Khan, 1973; Sellyei and Kelemen, 1971; Tough and Court-Brown, 1965).

Vigliani and Forni (1969) found a significant increase of peripheral blood lymphocyte chromosomal aberrations in workers exposed to benzene, but not in those exposed to toluene and xylene. Some of these aberrations persisted for several years after recovery from benzene hemopathy. The authors hypothesized that leukemia may develop in cases where a potentially leukemic clone of cells with selective advantage is produced as a response to benzene exposure. Forni, et al. (1971a) examined chromosomal aberrations in 34 workers in a rotogravure plant and 34 matched controls, and found a significantly higher number of both stable

and unstable aberrations in the 10 benzene-exposed workers but a normal number in the 24 toluene-exposed workers. Forni, et al. (1971b) found significantly increased stable and unstable chromosomal aberrations in 25 subjects who had recovered from benzene hemopathy. Most of these persisted for several years after cessation of exposure and recovery. A correlation between benzene exposure and chromosomal aberrations has been reported by Tough, et al. (1970) and Hartwich and Schwanitz (1972), in the latter case after "low levels" of benzene exposure.

A recent report (Kilian and Daniel, 1978) on 52 workers exposed to benzene for 1 month to 26 years (mean of 56.6 months) found chromosomal aberrations (chromosome breaks, dicentric chromosomes, translocations, and exchange figures) in peripheral lymphocytes at two to three times the rates found in controls. In this study the 8-hour average time-weighted benzene exposure was 2 to 3 ppm, the average concentration determined by 15-minute sampling was 25 ppm, and the peak concentration was 50 ppm.

Although the association between benzene exposure and hemopathy and/or chromosomal aberration is clear there is no correlation between the degree or length of exposure, the clinical symptoms, and the extent or persistence of chromosomal aberrations (U.S. EPA, 1977).

Carcinogenicity. Lignac (1932) reported the occurrence of leukemia in 8 of 33 albino mice subcutaneously injected with 0.001 ml benzene in 0.1 ml olive oil weekly for 17 to 21 weeks.

These results remain in question, however, since no controls were used (Int. Agency Res. Cancer, 1974). Kirschbaum and Strong (1942) found leukemia in 6/20 mice (30 percent) subcutaneously injected with 0.001 ml benzene in sesame oil weekly, compared with 29/212 (14 percent) in controls, the difference being not statistically significant. Amiel (1960) gave weekly subcutaneous injections of 0.001 ml benzene in 0.1 ml olive oil for life to AKR, DBA2, C3H, and C57BL6 mice, in groups of 30 males. No cancer was found in any mice of the DBA2, C3H, and C57BL6 strains. Eight of 30 treated AKR mice developed leukemia, as did 30/35 untreated AKR mice. Hiraki, et al. (1963) injected five female and five male mice with 0.1 ml of a 1 percent solution (0.087 mg) of benzene in olive oil each week. Two mice died in 8 weeks; the remaining eight mice were treated for 10 weeks. Of these, two males and three females developed subcutaneous sarcomas. Three of these tumors were transplantable into syngenetic mice. No controls were reported. Ward, et al. (1975) subcutaneously injected weanling male C57BL/6N mice twice weekly for 44 weeks and once weekly for the last 10 weeks, gradually increasing the dose from 450 mg/kg to 1.8 g/kg benzene. The mice were killed 104 weeks after the first injection, and no evidence of carcinogenic activity was found in either the benzene-treated or negative control mice. Butylnitrosourea induced leukemia, lymphomas, and/or intestinal neoplasms in almost all the positive controls.

Numerous studies on the effects of skin application of benzene to mice (many where benzene was the solvent control) have

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yielded negative results (Baldwin, et al. 1961; Burdette and Strong, 1941; Coombs and Croft, 1966; Kirschbaum and Strong, 1942; Laerum, 1973). Inhalation (Jenkins, et al. 1970; Wolf, et al. 1956) and oral (Wolf, et al. 1956) dosing likewise have yielded negative carcinogenic results. Recently Nelson (1977) has found leukemia in 2/40 CD-1 mice given lifetime exposures to 300 ppm benzene; one had chronic myelogenous leukemia and one had an acute, possibly myeloblastic, leukemia. A third mouse died of myeloid metaplasia. Nelson also found chronic granulocytic leukemia in 1/40 Sprague-Dawley rats given lifetime exposures to 100 ppm benzene.

Thus far, animal experiments do not support the view that benzene is leukemogenic. Ward, et al. (1975) suggested that benzene-induced leukemia in man may be a fairly rare event occurring only in highly sensitive individuals, because of genetic constitution, or because of synergistic action with other environmental agents. Another point suggested to explain the difference between man and animal models was a difference in metabolism of benzene (Natl. Acad. Sci./Natl. Res. Coun., 1976).

Despite essentially negative animal data, the evidence that benzene is a leukemogen for man is convincing and has recently been reviewed by Natl. Acad. Sci./Natl. Res. Coun. (1976), Natl. Inst. Occup. Safety Health (1977), and U.S. EPA (1977).

Over 250 cases of leukemia in benzene- exposed individuals have been reported in the literature since the original description by Delore and Borgomano in 1928, essentially all of them in an occupational setting (Benzene in the Work Environment, 1974). These case reports, however, do not establish benzene as a leukemogen because of the possibility of chance association, lack of information on the size of the population at risk, and chance of underreporting of benzene-associated leukemia due to acceptance of the relationship (thus inhibiting publication) or due to the lag period between exposure and onset of leukemia. These case reports do, however, suggest such leukemogenic properties. Conspicuous in these reports is the frequent description of persons suffering from benzene-associated pancytopenia in whom evolution to acute leukemia was observed. Idiopathic aplastic anemia is an uncommon disorder, reported far less frequently than acute myelogenenous leukemia. The relatively frequent documentation of benzene-associated pancytopenia progressing to acute leukemia, similar to that observed in other causes of aplastic anemia, further supports the possibility that exposure to benzene increases the risk of developing acute leukemia (U.S. EPA,1977).

Delore and Borgomano (1928) first described the association between benzene exposure and leukemia in a worker exposed to benzene for 5 years, who developed acute lymphoblastic leukemia. In 1939 two cases of leukemia among patients who had chronic benzene exposure in the industries around Boston were described (Bowditch and Elkins, 1939; Hunter, 1939; Mallory, et al. 1939).

One patient had been exposed to benzene for 10 years, 4 years heavily (200 ppm) and the succeeding 6 years lightly, but had shown hematologic evidence of benzene intoxication from the beginning of his employment. In the later 3 months of his life, the typical pattern of an acute myeloblastic leukemia developed. The characteristic findings of leukemia were found at autopsy which included diffused myeloid infiltration of the liver, spleen, and bone marrow. The other case was a 12-year-old boy, a painter's son, who used his father's paint shop to repaint toys, using a paint remover known to contain benzene. He developed aplastic anemia but sternal puncture and sternal biopsy revealed a typical leukemic replacement of the marrow with undifferentiated cells of the lymphoblastic series. DeGowin (1963) reported a case involving a painter who had been exposed to benzene for 13 years. He developed a hypocellular bone marrow and pancytopenia, followed by a relatively normal bone marrow with variable leukopenia, anemia, and thrombocytopenia. Then after 15 years a distinctly leukemic marrow and pancytopenia were found. Tareeff, et al. (1963) described six acute and 10 chronic leukemia cases in workers in the U.S.S.R. occupationally exposed to benzene for 4 to 27 years. In three of the acute cases a latent period of 2 to 5 years from cessation of exposure was noted.

Although case reports have suggested that benzene causes leukemia, convincing evidence has come from epidemiological studies. Many of these have come from Aksoy and his colleagues in Turkey (Aksoy, 1977; Aksoy, et al. 1972, 1974a,b, 1976a,b). They

described individual case reports of workers with aplastic anemia progressing through a preleukemic phase to acute myeloblastic leukemia or erythroleukemia; an accumulation of cases resulting in a statistically significant higher incidence of acute leukemia among shoe workers; and an outbreak of leukemia in this population that appears temporally related to the onset of benzene use and that has subsided following replacement of benzene as a solvent for adhesives.

Aksoy, et al. (1974b) observed 26 cases, during the period 1967-73, of acute leukemia among 28,500 shoe workers exposed to maximums of 210 to 650 ppm benzene for 1 to 15 (mean 9.7) years. Fourteen cases were acute myeloblastic leukemia, four preleukemia, three acute erythroleukemia, three acute lymphoblastic leukemia, one acute promyelocytic leukemia, and one acute monocytic leukemia. From these data they derived a leukemia incidence of 13 per 100,000, which is statistically significantly higher than the risk of 6 per 100,000 assumed for the general population. The latter figure is derived from leukemia incidence in more developed countries than Turkey and thus may be high. Aksoy (1977) recently estimated the incidence of leukemia in the general population of Turkey as 2.5 to 3.0 per 100,000. Moreover, if the relative incidence were computed solely for acute myeloblastic leukemia and its variants, a magnification of the risk in benzene-exposed shoe workers would be observed. Secondly, in their series the average age at the diagnosis was 34.2 years. This is a relatively low-risk age period for leukemia, with a reported death rate about half of the overall

incidence (Cooke, 1954). Recalculation of their data with an age factor would presumably increase the statistical significance of the findings (U.S. EPA, 1977). Thirdly, Aksoy (1977) believes that shoe workers with acute leukemia were probably admitted to other Istanbul hospitals without his knowledge.

Askoy, et al. (1976b) reported that, of 34 patients, six exposed to 150 to 210 ppm benzene vapor for up to 28 years (mean exposure: 11 years) were diagnosed as having Hodgkin's disease. Twenty other patients also exposed to benzene were later diagnosed as leukemics. Based on case studies, the authors stated that benzene, because of its toxicity to both the hematopoietic and reticuloendothelial system, is etiologically related to the onset of Hodgkin's disease. Alternatively, the authors proposed that benzene may act with other unknown factors contributing to the onset of this proliferative disorder.

Aksoy (1977) presented his observations of acute leukemia in shoe workers for the period 1967-76. These annual incidence data appear below:

1967	1	1972	5
1968	1	1973	7
1969	3	1974	4
1970	4	1975	3
1971	6	1976	0

The peak incidence (19.7 per 100,000) of leukemia in shoe workers occurred between 1971 and 1973. This follows by a few years the appearance of a notable incidence of aplastic anemia in this occupational group. The decline in cases since 1973 is temporally related to a decrease in use of benzene as an adhesive solvent, which began gradually in 1969. Aksoy also reports that pancytopenia was present in 27.5 percent of the cases before the onset of acute leukemia, which occurred 6 months to 6 years later. The hematological findings often indicated a period of recovery before the onset of leukemia, a phenomenon also noted by other investigators. Aksoy states that during this period, over 100 cases of aplastic anemia were observed that were either idiopathic or associated with an agent other than benzene, and in none of these cases did acute leukemia develop. He also states the opinion that no blood dyscrasia is required before the onset of leukemia and provides an example of a 23-year-old shoe worker who was hematologically normal when studied 4 years before the onset of acute erythroleukemia.

Vigliani and Saita (1964) estimated the number of workers exposed to benzene in northern Italy, and, based on the incidence of acute leukemia in the general population of Milan, calculated a twenty-fold higher risk of acute leukemia in these workers. More recently Vigliani and Forni (1976) summarized their experience from 1942 to 1975. During this period they observed 66 cases of significant benzene hematotoxicity in Milan, mostly in shoe workers; 11 of these were acute myelogenous leukemia. In Pavia during the period 1959-74 they observed 135 shoe workers

with benzene hematotoxicity, 13 with acute myelogenous leukemia. Benzene concentrations were usually 200 to 500 ppm. They also observed two cases of myelogenous leukemia in the rotogravure industry where ambient benzene exposures were calculated to be 200 to 400 ppm, with peaks up to 1,500 ppm.

Ishimaru, et al. (1971) performed a retrospective study of survivors of the two atomic bombings of Japan, evaluating the effects of occupation on the incidence of leukemia. Ten occupations were considered to involve exposure to benzene, and these occupations taken together were associated with an increased risk for leukemia (30 cases, 14 controls, relative risk = 2.3, PF0.01). Twenty-four leukemia cases were too far from the atomic bomb explosion for radiation to have influenced the increased risk. The increased risk, however, could be associated with exposures other than to benzene, as in none of the 10 occupations considered would benzene be the only chemical encountered. The risk was significantly higher in those with 5 or more years of potential exposure but not in those who had been employed in such occupations for less than 5 years. The relative risks were similar in Hiroshima and Nagasaki and were higher for acute leukemia (2.9) than for chronic leukemia (1.8).

Girard and Revol (1970) evaluated the frequency of a positive history of benzene exposure in 401 patients hospitalized with serious hematological disorders, compared with 124 patients hospitalized for other reasons. A statistically significant increase in history of benzene exposure was found in patients

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with aplastic anemia (10/48, 21 percent), acute leukemia (17/140, 12 percent), and chronic lymphocytic leukemia (9/61, 15 percent) compared with the control patients (5/124, 4 percent).

The Occupational Health Studies Group of the University of North Carolina has studied the health status of rubber-industry workers, a group exposed to various solvents including benzene (Andjelkovic, et al. 1976, 1977; McMichael, et al. 1974, 1975, 1976a,b; Tyroler, 1977). They have evaluated the 10-year mortality experience of a large cohort of male workers (5,106 deaths) at four tire manufacturing plants. The subjects were in the work force or were retired in 1964. The mortality due to all cancers (1,014) was normal or slightly elevated, depending on the data base used for comparison. Deaths due to cancer of the lymphatic and hematopoietic system (total of 109) were 31 percent higher than expected and were increased in cohorts of each of the four companies. In the category of lymphosarcoma and Hodgkin's disease, the standard mortality ratio (SMR) was 129 and an increase in the expected number of deaths was observed in two of the four company cohorts. Similarly, for deaths due to all forms of leukemia the SMR was 130 and the increase was observed in three of the four cohorts. When this latter category was further subdivided, the overall SMR for lymphatic leukemia was found to be 158 and the expected death rate was elevated in two of the four company cohorts. Of particular note is that the SMR for deaths attributed to lymphatic leukemia was 291 in the age group 40 to 64.

Several approaches were followed in further study of the increased incidence of lymphatic leukemia. Contrasting the work history of 17 patients with lymphatic leukemia with those of three matched controls for each case revealed that solvent exposure increased the overall risk by a factor of 3.25. Further classifying the groups according to high, low, and medium solvent exposure yielded a 5.5 factor for the high-exposure group. In those patients first subjected to high exposure between 1940 and 1960, the factor for the relative risk of lymphatic leukemia was 9.0. The relationship of solvent exposure to lymphatic leukemia was statistically significant at PF0.025. The study also showed an increase in the mean difference in years of work history between lymphatic leukemia and the case controls. This was inversely proportional to the extent of solvent exposure. A limitation is the lack of historical data concerning the benzene exposure or the concentrations of other solvents, e.g., xylene, toluene, and trichloroethylene. These studies do, however, strongly support the possibility that long-term exposure to benzene in the U.S. rubber industry leads to an increased risk of lymphatic leukemia (U.S. EPA, 1977).

Monson and Nakano (1976a,b) evaluated a cohort of 13,571 white male rubber workers and found a SMR of 128 for leukemia.

Thorpe (1974) surveyed 38,000 workers in eight European affiliates of a major petroleum company to determine the incidence of leukemia in persons potentially exposed to benzene at low levels for 10 years. The data revealed no statistically

significant increase in the leukemia rate over that expected in the population. There was, however, a tendency toward a higher rate in the benzene-exposed as compared with the unexposed workers. The case-finding techniques of this study were criticized by Brown (1975).

The most convincing epidemiological study implicating benzene as a leukemogen is the recent one by Infante, et al. (1977) from National Institute for Occupational Safety and Health. They followed for vital status, up to mid-1975, 748 white males exposed to benzene in the manufacture of a rubber product from 1940 through 1949. A statistically significant ($P < 0.002$) excess of leukemia was found in comparison with two control populations, the general American population and another industry not using benzene. There was a fivefold excessive risk of all leukemias and a tenfold excessive risk of myelocytic and monocytic (probably myelomonocytic) leukemias combined. The single case of chronic myelocytic leukemia had a lag period of 2 years from initial benzene exposure, but the six cases of acute myelocytic and monocytic leukemia had lag periods of 10 to 21 years. The true leukemia risk to benzene-exposed workers was thought to be much higher because the follow-up of the study population was only 75 percent complete, and the remaining 25 percent were all regarded, in the calculations, as being alive at the end of the study period. The environment of the workers was not contaminated with any solvents other then benzene, and benzene concentrations in the air were generally below the recommended limit in effect during the period of the study, i.e.,

100 ppm (1941), 50 ppm (1947), 35 ppm (1948), 25 ppm (1957), and 10 ppm (1969). In general, this epidemiological study provides excellent confirmatory evidence of the causal relationship of benzene exposure to acute myelocytic leukemia (U.S. EPA, 1977).

Ott, et al. (1978) recently studied the mortality experience of 594 workers exposed to benzene in the chemical industry. The workers were stratified by benzene exposure levels, and hematological findings carefully examined. The cause-specific mortality rates for the 102 deceased individuals agreed well with those observed in a study of over 8,000 other employees in the same area. No association with benzene exposure was detected; however, two deaths due to acute myelogeneous leukemia, and one with myeloblastic leukemia listed as a significant associated condition, occurred. The time-weighted average benzene exposure of these three individuals was below 10 ppm. The expected number of myelogenous leukemia cases in this study population is 0.8, and the observed number of three is only of marginal statistical significance. These inconclusive findings may be due to the small number of deaths evaluated in the study (U.S. EPA, 1977).

With reference to the quantitative relationship of benzene exposure level to the development of acute leukemia, the available literature is inadequate for the generation of dose-response curves (U.S. EPA, 1977). In contrast with pancytopenia, where a large percentage of benzene-exposed individuals have developed benzene hematotoxicity and thus the available

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monitoring information might be used to estimate the average benzene exposure, leukemia occurs in a very small percentage of the benzene-exposed, and those developing leukemia may have been exposed to higher concentrations than indicated by area-wide monitoring systems. This exposure might occur because of the specific job involved or faulty work habits, e.g., failure to wear a respirator. In those studies of acute leukemia where benzene exposure levels have been reported, the concentrations have generally been above 100 ppm (Aksoy, et al. 1972, 1974a,b, 1976a,b; Vigliani and Forni, 1976; Vigliani and Saita, 1964; Kinoshita, et al. 1965; Sellyei and Kelemen, 1971). The often-reported longer period of benzene exposure required for the development of acute leukemia than for pancytopenia might well be a spurious consequence of the frequent lag period between the initiation of benzene exposure and the development of acute leukemia.

Also reported in association with benzene exposure have been lymphosarcoma (Bousser, et al. 1948; Caprotti, et al. 1962), Hodgkin's disease (Aksoy, et al. 1974c; Mallory, et al. 1939), reticulum cell sarcoma (Paterni and Sarnari, 1965), and multiple myeloma (Tareeff, et al. 1963; Torres, et al. 1970), but none of these case reports suggests other than a chance relation to benzene exposure (U.S. EPA, 1977).

CRITERION FORMULATION

Existing Guidelines and Standards

Existing air standards for occupational exposure to benzene include 10 ppm (32 mg/m^3) and an emergency temporary level 1 ppm by the U.S. Occupational Safety and Health Administration (Natl. Inst. Occup. Safety Health, 1974; 1977), 25 ppm (80 mg/m^3) by the American Conference of Governmental Industrial Hygienists (1971), 16 ppm promulgated by Czechoslovakia in 1969, and 6 ppm (20 mg/m^3) promulgated by the Soviet Union in 1967. OSHA also prohibits repeated or prolonged skin exposure to liquid benzene. No standard for benzene in water exists, but Cleland and Kingsburg(1977), using several assumptions and ACGIH air standards, have suggested values of 1,071 and 414 µg/l for ingested water, and 107 µg/l for ingested water based on the potential carcinogenicity of benzene.

Current Levels of Exposure

As discussed previously under "Exposure," the major source of human exposure to benzene is through the respiratory route. The annual average exposure of an individual to ambient benzene from all air sources is 1.03 ppb (Mara and Lee, 1977).

The U.S. EPA (Mitre Corp. November 1978) has attempted to put into perspective the known and unknowns about total benzene exposure for its National Drinking Water Program. Based upon the assumptions utilized, air was the predominant source of benzene absorbed by the general population. This source

contributed more than 80 percent of the total daily benzene uptake for an adult male living in an urban environment. Assumed benzene content in drinking water included levels 0.1, 0.2, 1 and 10 µg/l, food was 250 µg/l and ambient air was 50 µg/m3. The total daily intake at the 10 µg/l benzene level for drinking water was 1.128 mg/day of which 1.4 percent came from the water, 17.7 percent came from food and 80.9 percent came from ambient air exposure.

As shown by Mara and Lee (1977) certain occupational groups have potential exposure to benzene over and above the ambient levels. The representative industry activities include chemical manufacturing, coking operations, gasoline service stations, petroleum refineries and solvent operations.

Special Groups at Risk

There is some suggestion that there may be a genetic predisposition to benzene toxicity; this subject is reviewed by Goldstein (1977b). Although there are many more cases of benzene-induced hematotoxicity in males than in females because of occupational exposure, there is evidence to suggest that exposed females have a greater chance of developing severe disease (Mallory, et al. 1939; Ito, 1962). Age does not seem to affect hematotoxicity (Aksoy, et al. 1971).

Basis and Derivation of Criterion

The Natl. Acad. Sci./Natl. Res. Coun. (1977), in its review of drinking water and health, concluded that existing animal and human data did not allow the establishment of limits for benzene in drinking water. This was because the animal results were not statistically significant and were based on non-oral administration of benzene. In addition,

the occupational studies on human exposure did not contain adequate information on degree of exposure or size of the population at risk, and did not rule out exposure to other chemicals besides benzene.

Since the publication of the Natl. Acad. Sci./Natl. Res. Coun. report, the above-described epidemiological studies by Aksoy (1977), Infante, et al. (1977), and Ott, et al. (1978) have appeared. These studies include information on degree of benzene exposure and size of the population at risk, and rule out exposure to solvents other than benzene. The U.S. EPA Carcinogen Assessment Group (1978) has made use of these three occupational studies to calculate a leukemia dose-response curve. The slope of this curve is 0.024074, in units of lifetime risk of leukemia per ppm exposure to benzene in air. Since 1 ppm is 3.25 mg/m^3, and assuming a respiratory rate of about 24 m^3/day, the benzene intake per individual at 1 ppm is:

$$(3.25\ mg/m^3)(24 m^3/day) = 78\ mg/day$$

To calculate the benzene intake resulting in a lifetime risk of leukemia of 10^{-5}, one solves the following equation for x,

$$\frac{x}{10^{-5}} = \frac{78\ mg/day}{0.024074}$$

Resulting in 0.032 mg/day.

The U.S. EPA (Mitre Corp., 1978) total exposure analysis indicates that the total body exposure may be as high as 1.1 mg/day of benzene. This was derived using estimates which have varying degrees of support in terms of hard data.

The specific use of the total exposure estimates for calculation of water criterion does not seem warranted at this particular time because of a general lack of knowledge about the accuracy of the estimates. It can be said, however, that from a general weight of evidence perspective, it appears that air exposure may contribute the majority of total exposure. The total exposure consideration should be factored into the criterion development at a later date when additional data is available.

Under the Consent Decree in NRDC v.Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Benzene is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of benzene in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of benzene corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for

every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, 10^{-7} as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish. (2)	0	0.15 µg/l	1.5 µg/l	15 µg/l
Consumption of fish and shellfish only.	0	2.5 µg/l	25 µg/l	250 µg/l

(1) Calculated by applying a modified "one-hit" extrapolation model described in the Methodology Document to the human epidemiology data presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentration corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Six percent of the benzene exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 6.9 fold. The remaining 94 percent of benzene exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of benzene, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding benzene concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding benzene concentrations.

Although total exposure information for benzene is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into ambient water quality criteria formulation until additional analysis can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

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Appendix I

Derivation of Criterion for Benzene

Three epidemiology studies of workers exposed to benzene vapors on their jobs, performed by Infante, Ott, and Askoy, were reviewed by the CAG for the Office of Air Quality Planning and Standards (Albert, 1978). Their result was that the potency for humans breathing benzene continuously is B = 0.02407. This means that the lifetime risk of getting leukemia, R, equals 0.024074 times the lifetime average continous exposure, X, measured as ppm of benzene by volume in air, or R = B X. Therefore the air concentration, X, resulting in a risk of 10^{-5} is X = R/B = 10^{-5}/.024074 = 4.1539 x 10^{-4} ppm.

Since the air concentration corresponding to 1 ppm of benzene is 3.25 x 10^{-3} $\mu g/m^3$ and since people breathe an average of 24 m^3/day of air, the daily intake that would result in a risk of 10^{-5} is:

4.154×10^{-4} ppm x 3.25×10^{3} mg/m^3 per ppm x 24 m^3/day = 32.4 μg/day

If it is assumed that the fraction of benzene intake reaching the target site is the same via inhalation and ingestion of water and fish, a daily benzene intake of 32.4

5860
479

µg through drinking water and fish alone would also cause a leukemia risk of 10^{-5}. The water concentration giving this intake is:

$$C = (32.4\ \mu g/day)/(2 + 6.9\ (0.0187)$$

$$= 15.22\ \mu g/l$$

$$= 15\ \mu g/l$$

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